

AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph beginning at page 1, line 21 with the following amended paragraph:

The denatured lipoprotein strongly suggests the association thereof with various diseases of the circulatory system including such diseases of coronary artery system as cardiac infarction and stenocardia, such diseases of the cerebral arteries as cerebral infarction and cerebrovascular dementia, such diseases of the renal arteries as nephropathy and diabetic nephropathy, and such diseases of the peripheral artery system as obstruction of peripheral arteries. The standard substance for determining mass of denatured lipoprotein and the various experimental reagents for investigation of physiological role and physiological activity of the denatured lipoprotein, therefore, constitute themselves very important substances that affect the results of the research efforts. The denatured lipoprotein which has been stabilized in the manner described above, therefore, is useful as a standard substance in a method for determining denatured lipoprotein content in a blood component as by causing the denatured lipoprotein to contact an antibody capable of recognizing the denatured lipoprotein and determining the reactivity of the antibody with a sample and as ~~a varying an~~ experimental reagent for investigating the physiological role and physiological activity of the denatured lipoprotein.

Please replace the paragraph beginning at page 3, line 11 with the following amended paragraph:

The fact that it is difficult to obtain the standard substances necessary for the determinations performed in such experiments, however, has complicated the situation. For the purpose of investigating the physiological role of denatured lipoprotein, it becomes necessary to collect a large number of ~~denatured lipoproteins from sera blood samples denatured lipoprotein from a plurality of installation~~ and compare them. For the comparison, it is essential that the measurements obtained in the individual tests be free from variation. No reproducibility can be ensured among these measurements unless a

standard substance stable and excellent in reproducibility throughout a duration necessary for a series of relevant tests is available. When the test results are markedly varied among different persons who measure owing to the use of different standard substance, the interpretation of the physiological role of given denatured lipoprotein is no complicated as to render it impossible to obtain a fixed conclusion. This inability to obtain a standard substance which fits stable preservation has closed the way of applying the determination of the amount of denatured lipoprotein present in a given sample, for example, as a means to judge a disease exactly despite popular recognition of the physiological importance of this determination.

Please replace the paragraph beginning at page 4, line 2 with the following amended paragraph:

Generally, in the determination of the mass of protein contained in blood serum, for example, the practice of stabilizing by some method or other what may be called a standard blood serum or a target component in an isolated state and using the product of this stabilization as a standard substance is now carried out. As regards the lipoprotein in general, a method for producing standard blood plasma or standard blood serum stable during prolonged preservation by optionally mixing lipoprotein-containing blood plasma or blood serum with such nonreducing sugar as sucrose and freeze-drying the resultant mixture till the water content reaches a level in the range of 1-10 mass% (Patent publication EP-A-617289) and a method for commercially producing a stable freeze-dried product by ~~obtaining reconstructive lipoprotein from apolipoprotein and lipid and~~ freeze-drying and stabilizing reconstructed lipoprotein, prepared from apolipoprotein and lipid, ~~the reconstructive lipoprotein~~ in the presence of a stabilizer such as sucrose or mannitol (Patent publication US-A-5,652,399 5,652,339) have been reported. The patents published in these official gazettes merely attempt to stabilize lipoprotein as a means to stabilize the lipoprotein without entailing denaturation thereof and do not disclose the stabilized denatured lipoprotein and a method for the production thereof.

Please replace the paragraph beginning at page 5, line 4 with the following amended paragraph:

In view of this state of affairs, Patent publication JP-A-09-288,106 has disclosed a method for determining human oxidized lipoprotein by using as a standard what is produced by incorporating ~~into blood plasma~~ lipoprotein the oxide of phospholipid obtained by artificially oxidizing phospholipid into lipoproteins of blood plasma. The standard substance which is used in the method described above, however, is so deficient in stability of preservation as to require the individual preparation thereof prior to each use and entail a complicated procedure.

Please replace the paragraph beginning at page 5, line 17 with the following amended paragraph:

Therefore objects of the present invention are to provide denatured lipoprotein excelling in stability of prolonged preservation[[]]; namely, the lipoprotein does not cause any discernible variation in the determination[[]] throughout the duration of preservation and a method of the production thereof, wherein the lipoprotein is applied as a standard substance for the determination of the mass of denatured lipoprotein contained in a given blood component or as ~~a varying an~~ experimental reagent for the investigation of physiological role of denatured lipoprotein.

Please replace the paragraph beginning at page 5, line 28 with the following amended paragraph:

The present inventors, as a result of a diligent study pursued with a view to attaining the object mentioned above, have found that by freeze-drying ~~such~~ artificially denatured lipoproteins [[]], it is made possible to improve significantly such denatured lipoproteins in stability of prolonged preservation and consequently accomplish the object of the present invention. Denatured lipoproteins include oxidized lipoproteins obtained by ~~oxidizing~~ oxidation of [[]] lipoproteins as egg-yolk, milk, whole blood, blood-serum, and blood-plasma ~~severally containing lipoprotein, lipoprotein-fractions~~

~~partially-fractioned therefrom, and lipoproteins which are fractionally purified by the ultracentrifugal separation technique, by the use of with a catalyst represented by [[such]] a metal ion such as a copper ion[[:]], acetylated lipoproteins obtained by acetylating acetylation of the above-mentioned lipoproteins with acetic anhydride etc. [[:]], [[or]] and malondialdehyde-conjugated modified lipoproteins obtained by reacting the above-mentioned modification of lipoproteins with malondialdehyde etc. [[:]]. it is made possible to improve conspicuously such denatured lipoproteins in stability of prolonged preservation and consequently accomplish the object of the present invention; Sources containing lipoproteins include egg yolk, milk, whole blood, blood serum, blood plasma, lipoprotein samples obtained by partial fractionation or by partial purification via, e.g., ultracentrifugation. The present inventors have also found that by allowing the presence of sucrose, lactose, trehalose, bovine blood serum albumin (BSA), or human blood serum albumin (HAS) etc. as stabilizer during the course of freeze-drying, it is made possible to improve the denatured lipoprotein to a greater extent in stability of prolonged preservation and give a better solution to the problems mentioned above.~~

Please replace the paragraph beginning at page 6, line 20 with the following amended paragraph:

The present inventors, after a diligent study pursued with a view to accomplishing the object mentioned above, have found that by performing a process including at least one freezing operation on a solution containing lipoprotein thereby denaturing the lipoprotein contained in the solution, it is made possible to obtain a standard substance usable for the determination of a denatured protein content in a given blood sample or a varying an experimental reagent usable for the investigation of physiological role or physiological activity of the denatured protein. They have further found that by freeze-drying the denatured lipoprotein obtained as described above, it is made possible to improve prominently the stability of prolonged preservation of the denatured lipoprotein in the dried state and the stability of preservation of the denatured lipoprotein in the dried state after it has been dissolved into a solution and consequently accomplish the object of

Applicant(s) : Takashi Shigematsu et al.,
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the present invention. Here again, the present inventors have further found that by allowing the presence of sucrose, lactose, trehalose, bovine blood serum albumin (BSA), or human blood serum albumin (HAS) etc., as a stabilizer during the course of freeze-drying, it is made possible to improve the denatured lipoproteins to a greater extent in stability of prolonged preservation and give a better solution to the problems mentioned above.